

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 45 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

REMARKS

Reconsideration of this application is respectfully requested.

After entry of the complete listing of the claims provided above:

Claims previously pending: Claims 3144-3286.

Claims currently amended: Claims 3144-3147, 3150-3151, 3154-3155, 3157-3159, 3161-3169, 3172-3175, 3179, 3182-3183, 3185-3187, 3189, 3191-3195, 3197-3201, 3205, 3208-3209, 3211-3224, 3227-3228, 3231-3232, 3234-3238, 3241-3248, 3252-3256, 3258-3268, 3271-3277 and 3279-3283.

Claims currently canceled: Claims 3148-3149, 3156, 3170-3171, 3176-3178, 3184, 3202-3203, 3210, 3225-3226, 3233, 3239, 3249-3251, 3257, 3269-3270, 3278 and 3284-3286.

Claims previously canceled: Claims 1-3143.

Claims currently added: Claims 3287-3407.

Claims presently presented: Claims 3144-3147, 3150-3155, 3157-3169, 3172-3175, 3179-3183, 3185-3201, 3204-3209, 3211-3224, 3227-3232, 3234-3238, 3240-3248, 3252-3256, 3258-3268, 3271-3277, 3279-3283 and 3287-3407.

Entry of the above claim listing and claim amendments is respectfully requested.

Applicants wish to thank Supervisory Patent Examiners Ardin H. Marschel, Ph.D, and Michael Woodward, Ph.D, Training Quality Assurance Specialist, for the time and courtesy which they extended to Applicants' undersigned attorney and their two legal representatives, Eugene C. Rzucidlo, Esq. and Robert M. Schulman, Esq. during the interview held at the U.S. Patent Office on February 17, 2004. As indicated in the Interview Summary [Form PTOL-413 (Rev. 04-03)], Applicants presented a number of proposed claim amendments and other sheets for the purpose of addressing the issues raised in the November 26, 2004 Office Action.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 46 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

I. Summary of February 17, 2005 Interview

Applicants' representatives and their undersigned attorney presented new claim language for the solid support claims, presently pending as claims 3144 and 3145. Three sheets were presented and made of record for claims designated 3144, 3145 and 3145X. Applicants' representatives pointed out that the inclusion of "one or more amine(s), hydroxyl(s) or epoxide(s)" in the proposed language for claims 3144 and 3145 for fixing the nucleic acid to the non-porous solid support distinguished the present invention from Stuart et al., U.S. Patent No. 4,732,847. The Examiner hypothesized that the glass slide disclosed in Stuart's '847 Patent might provide a hydroxyl group for attaching a nucleic acid. Applicants' representatives and attorneys responded that the SiO₂ present in glass generally could be converted into a functional hydroxyl group capable of bonding to a nucleic acid only by extraordinarily harsh treatment conditions, such as boiling hydrochloric acid [see, for example, Cohen et al., "Covalent attachment of DNA oligonucleotides to glass," Nucleic Acids Research 25(4):911-912 (1997); copy attached as Exhibit A]. Stuart however was completely silent as to such conditions. Indeed, quite to the contrary, Stuart discloses use of a mild acid, such as acetic acid, for treatment of a slide. It is usually safe to assume that persons skilled in the art do not carry out extraordinary treatments, such as use of boiling concentrated HCl unless such conditions are viewed as necessary to achieve a desired end. Accordingly, the inference one can draw by use of such treatment in the afore-described Cohen publication supports the idea that a milder and cooler acid would not have sufficed.

Applicants' representatives also argued that the covalent attachment to the nucleic acid of either (1) a signaling moiety or (2) a bridging moiety (which bridging moiety is covalently or non-covalently attached to a signaling moiety) distinguished the invention of claim 3145X from Stuart's '847 Patent. Some discussion followed regarding the covalent attachment limitation in claim 3145X and as to whether it sufficiently distinguished the claimed subject matter from Stuart's disclosure.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 47 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Applicants pointed out that, as claimed, there was always a moiety covalently attached to the nucleic acid strand (either the signaling moiety itself or the bridging moiety) in contrast to Stuart who provided no moiety covalently attached to the nucleic acid.

Applicants' attorneys presented several sheets directed to new matter rejections and the two vagueness/indefiniteness rejections. Applicants' claims proposed for addressing these rejections were set forth in several sheets designated Exhibits 1B, 3, 5, 10 and 11. Arguments addressing other rejections were provided in other sheets designated Exhibits 1A, 1C, 2, 4, 6 and 9.

In further detail, Exhibit 1A listed the number of different contexts in which "well" or "wells" are disclosed in the specification (herein referred to as the "'070 specification"). Applicants' attorneys asserted that these several descriptions as listed in Exhibit 1A supported claims directed to a "generic well or wells."

In Exhibit 1B, Applicants' attorneys presented proposed wording for claim 3147, indicating that the term "set" had been replaced by "arrangement," but only in the context of "wells, tubes or cuvettes." A discussion ensued whether to amend proposed claim 3147 (Exhibit 1B) to recite "a plate or plates, a well or wells, a microtiter well or microtiter wells, a depression or depressions, a tube or tubes, a cuvette or cuvettes, a bead or beads, or an arrangement of said wells, tubes or cuvettes."

In Exhibit 1C, Applicants' attorneys presented citations in the '070 specification that support a "generic plate or plates."

In Exhibit 2, Applicants' attorneys presented citations in the '070 specification to support the claim language for "more than one surface." The Examiner pointed out that such claim language did not further limit the subject matter of the "solid support" because a solid support would have at least two surfaces. Applicants' attorneys responded that consideration would be given to possibly canceling claims carrying the "more than one surface" limitation.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 48 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) – May 25, 2005]

In Exhibit 3, Applicants' attorneys presented proposed wording for claim 3149 in which the nucleic acid is said to be "fixed or immobilized to said reactive sites or binding sites."

In Exhibit 4, Applicants' attorneys presented two citations that would support the "proportional to" quantitation limitation in the claims. A discussion followed whether the two disclosures supported the "proportional to" limitation beyond the cited radiolabeled probes. It was pointed out that in the first citation (page 4, last full paragraph), the sentence citing "radiolabeled probes" begins with the introductory phrase, "in such systems." Further, the following sentence refers to "proportional techniques," [including], for example, competitive immunoassays." Combined with the second citation (page 11, first paragraph) that refers to a "quantifiable report of the relative amount of analyte present," there seemed to be consensus at the interview that the "proportional to" claim limitation is supported by the '070 specification.

In Exhibit 5, Applicants' attorneys presented proposed language for claim 3165 in which the non-radioactive chemical label is said to be quantifiable "from said solid support."

In Exhibit 6, Applicants' attorneys addressed the terms "iminobiotin," "hapten" and "ligand." Exhibit 6 lists on two pages the references to these three terms as culled from European Patent Application Publication No. 0 063 879 which is cited in the paragraph bridging pages 7 and 8 in the '070 specification.

In Exhibit 9, information from the '070 specification was presented by Applicants' attorneys to show that the *in situ* disclaimer language was applicable to the array claims reciting wells or depressions. Exhibit 9 quotes from the '070 specification (page 10, first full paragraph). Applicants' attorneys explained that the *in situ* language applies to claim 3222 because the '070 specification (page 10, first full paragraph) describes the present invention as encompassing "indirect fixation of the analyte, such as in situ techniques where the cell is fixed to the

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 49 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

support." Because claim 3222 recites an array of various single-stranded nucleic acids fixed or immobilized to a non-porous support having wells or depressions, indirect fixation, such as *in situ* techniques generally applies to the subject matter claimed therein. Thus, the *in situ* disclaimer language applies to claim 3222 and all dependent claims thereof.

In Exhibit 10, Applicants' attorneys presented proposals for claims 3170 and 3171. As set forth in Exhibit 10, these claims both recite "Non-porous solid supports . . .," the earlier language to a "set" having been deleted.

In Exhibit 11, Applicants' attorneys presented proposed changes to the language in claims 3144 and 3173. In proposed claim 3144, the phrase "directly or indirectly" has been inserted before "immobilized," the term "indirectly" has been inserted before "immobilized," and the term "indirect" has been inserted before immobilization. In proposed claim 3173, the term "indirectly" has been inserted before "immobilized," and the term "indirect" has been inserted before "immobilization."

Regarding the array claims, Applicants' attorneys noted that the '070 specification discloses an array of various denatured analytes fixed to the wells (or depressions) of glass plates, and that these are described "for example." Further, in the first two pages of the '070 specification, "analyte" is defined in terms of "a substance or substances, alone or in admixtures." Thus, the term "various nucleic acids" is supported by the definition of "analyte," the latter including admixtures, and biological systems containing nucleic acids, such as viruses, cells, groups of cells. Applicants further referred the Examiner to the definition of "analyte" appearing in the paragraph bridging pages 1-2 of the originally filed application and noted two things. First, the definition included "A substance or substances, either alone or in admixtures" thereby making it clear that although used in the singular, the term clearly was intended by applicants to convey both single and different analytes. Second, the definition further discussed, as an example "a biological

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 50 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

system containing nucleic acids, such as a virus, a cell, or group of cells." As the Examiner acknowledged, such system of necessity would include different or various nucleic acids. The Examiner also acknowledged that in his experience, he had never seen the term admixture to relate to a combination of two or more of the same entity. The Examiner suggested that the term "mixture" might be used instead of "various." Applicants' attorney responded by indicating that the actual "various" term used in the '070 specification would be more acceptable.

The interview closed with the Examiners requesting that the various exhibits presented by Applicants' attorney and representatives be made part of the record. Copies were provided to the Examiners.

II. Claim Amendments

As indicated above, a number of changes to the claims in this application have been made.

Claims 3144-3171 (Solid Support)

These claims are directed to a non-porous solid support. As indicated above, independent claim 3144 was presented at the February 17, 2005 interview, and the same language is reflected in the claim listing. As set forth above, claim 3144 recites "[a] non-porous solid support comprising ***one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one single-stranded nucleic acid *is* fixed or immobilized in hybridizable form ***to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).***" Thus, language reciting "directly or indirectly," and disclaiming *in situ* has been deleted from claim 3144.

Claim 3145 is also independent and it recites "[a] non-porous solid support comprising ***one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one double-stranded nucleic acid *is* fixed or immobilized ***to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s), and wherein***

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 51 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

one nucleic acid strand of said *at least one* double-stranded nucleic acid *has covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety.*"

Directing attention to other dependent claims in the set:

Claim 3146 now depends from claims 3144, 3145, 3287, 3324 and 3325.

Claim 3147 now depends from claims 3144, 3145, 3287, 3324 and 3325 and it has been amended to recite "wherein said non-porous solid support comprises a plate *or plates*, a well or wells, a microtiter well or microtiter wells, *a depression or depressions, a tube or tubes, a cuvette or cuvettes, or a bead or beads.*"

Claims 3148-3149 have been canceled.

Claim 3150 now depends from claims 3287 and 3325, and now reads "[t]he non-porous solid support of claim *3287 or 3325 comprising* one or more amines."

Claim 3151 now depends from claims 3144, 3145, 3287, 3324 and 3325.

Claims 3154-3155 now depend from 3144, 3145, 3287, 3324 and 3325 and have been further amended to delete "direct or indirect."

Claim 3156 has been canceled.

Claim 3157 now depends from claims 3145, 3287 and 3325, and now recites, "The non-porous solid support of *claims 3145, 3287 or 3325*, wherein one strand of said *at least one* double-stranded nucleic acid is fixed or immobilized to said non-porous solid support *and the other strand of said at least one double-stranded nucleic acid is hybridized to said one strand.*

Claim 3158 now depends from claims 3144 and 3324, and has been further amended to recite, "said nucleic acid *is* DNA." Claim 3159 now depends from claims 3145, 3287 and 3325 and has been further amended to recite, "said nucleic acid *is* DNA."

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 52 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3161 now depends from claims 3145 and 3287, and has been further amended to recite, "said ***at least one*** double-stranded nucleic acid..."

Claim 3162 now depends from claims 3144 and 3324.

Claim 3163 now depends from claims 3144, 3145, 3287, 3324 and 3325.

Claim 3164 now depends from claims 3145 and 3287, and has been further amended to delete "non-radioactive chemical label," and now recites, "non-radioactive signaling moiety."

Claim 3165 now depends from 3145 and 3287, and now reads, "The non-porous solid support of ***claims 3145 or 3287***, wherein said non-porous solid support is transparent or translucent, and said ***non-radioactive signaling moiety*** is quantifiable in or from a fluid or solution or ***from*** said non-porous solid support, said quantity being proportional to the amount or quantity of said ***non-radioactive signaling moiety***."

In claim 3166, the last three recited members of the non-radioactive chemical label ("iminobiotin, a hapten or a ligand") have been deleted from the claim language. The claim now reads, "The non-porous solid support of ***claims 3145, 3287 or 3325***, wherein said ***non-radioactive signaling moiety*** comprises a chromagen or a chromagenic compound."

Claim 3167 now depends from 3145, 3287 and 3325, and now recites, "The non-porous solid support of ***claims 3145, 3287 or 3325***, wherein a non-radioactive signal from said ***non-radioactive signaling moiety*** is quantifiable or detectable by photometric techniques."

Claims 3168 and 3169 have been amended to change their claim dependencies.

Claims 3170 and 3171 have been canceled.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 53 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claims 3172-3197 (System)

These claims are directed to a system comprising a non-porous solid support in which nucleic acid is fixed or immobilized thereto. Claims 3172 and 3173 are independent system claims and follow the language of independent solid support claims 3144 and 3145 previously discussed. As now presented, claim 3172 recites "[a] system comprising a non-porous solid support ***which comprises one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one single-stranded nucleic acid ***is*** fixed or immobilized thereto in hybridizable form ***to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).***" As in the case of claim 3144, the language reciting "directly or indirectly," and disclaiming *in situ* has been deleted from claim 3172.

Claim 3173 now recites "[a] system comprising a non-porous solid support ***which comprises one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one double-stranded nucleic acid ***is*** fixed or immobilized ***to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s), and*** wherein one nucleic acid strand of said double-stranded nucleic acid ***has covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety.***" Thus, language describing a "non-radioactive chemical label which is quantifiable or detectable," and disclaiming *in situ* has been deleted from claim 3173 in favor of the present wording.

Directing attention to other dependent claims in the set, most if not all of the dependent system claims have been amended in a similar fashion as the dependent solid support claims discussed above.

Claim 3174 now depends from claims 3172, 3173, 3279, 3280, 3281 and 3282, and it recites "wherein said non-porous solid support comprises glass or plastic."

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 54 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3175 also now depends from claims 3172, 3173, 3279, 3280, 3281 and 3282, and it recites "wherein said non-porous solid support comprises a plate *or plates*, a well or wells, a microtiter well or microtiter wells, *a depression or depressions*, *a tube or tubes*, *a cuvette or cuvettes*, *or a bead or beads*."

Claims 3176-3178 have been canceled.

Claim 3179 now depends from claims 3172, 3173, 3279, 3280, 3281 and 3282.

Claims 3182 and 3183 also now depend from claims 3172, 3173, 3279, 3280, 3281 and 3282, and the "direct or indirect" language has been deleted from both claims.

Claim 3184 has been canceled.

Claim 3185 has been amended to depend from claims 3173, 3281 and 3282, and now recites "wherein one strand of said double-stranded nucleic acid is fixed or immobilized to said non-porous solid support *and the other* nucleic acid strand *of said double-stranded nucleic acid is hybridized to said one strand*." Thus, the word "indirect" and references to "sandwich hybridization" and complementary hybridization have been deleted from claim 3185.

Claim 3186 now depends from claims 3172 and 3280, and it has been amended to recite that "said nucleic acid *is* DNA." Claim 3187 now depends from claims 3173, 3281 and 3282, and it presently recites that "said nucleic acid is DNA."

Claim 3189 now depends from claims 3173 and 3288, and it has been further amended to recite "wherein one strand of said *at least one* double-stranded nucleic acid comprises a nucleic acid sequence of interest sought to be identified, quantified or sequenced."

Claim 3191 now depends from claims 3172, 3173, 3279, 3280, 3281 and 3282.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 55 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3192 now depends from claims 3173 and 3288, and phrase "non-radioactive chemical label" has been deleted in favor of ***non-radioactive signaling moiety***."

Claim 3193 also now depends from claims 3173 and 3288, and it recites that the "***non-radioactive signaling moiety*** is quantifiable . . . ***from*** said non-porous solid support, said quantity being proportional to the amount or quantity of said ***non-radioactive signaling moiety***."

Claim 3194 has been amended and now depends from claims 3173, 3281 and 3282. Further, this claim recites "wherein said ***non-radioactive signaling moiety*** comprises a chromagen or chromagenic compound." Thus, several members of such non-radioactive signaling moiety have been deleted from claim 3194.

Claim 3195 now depends from claims 3173, 3281 and 3282. As amended, claim 3195 recites that the ***non-radioactive signaling moiety*** is quantifiable or detectable by photometric techniques. Thus, reference to other techniques has been deleted from claim 3195.

Claim 3197 now depends from claims 3173, 3281 and 3282.

Claims 3198-3221 (Array)

These claims are directed to an array comprising various nucleic acids. Claims 3198 and 3199 are independent. Claim 3198 recites in its amended form "[an] array comprising various single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support." Thus, language for "directly or indirectly" and disclaiming *in situ* has been deleted from claim 3198.

As amended above, claim 3199 now recites "[an] array comprising various double-stranded nucleic acids fixed or immobilized to a non-porous solid support, wherein at least one nucleic acid strand of said various double-stranded nucleic acids comprises at least one non-radioactive ***signaling moiety*** which is quantifiable

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 56 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

or detectable." In addition to changing "chemical label" to *signaling moiety*, the "directly or indirectly" language and *in situ* disclaimer have been deleted from claim 3199.

Claim 3200 now depends from claims 3198, 3199, 3300, 3301, 3326 and 3327.

Claim 3201 similarly depends from claims 3198, 3199, 3300, 3301, 3326 and 3327, and it now recites "wherein said non-porous solid support comprises a plate *or plates*, a well or wells, a microtiter well or microtiter wells, *a depression or depressions, a tube or tubes, a cuvette or cuvettes, or a bead or beads.*"

Claims 3202 and 3203 have been canceled.

Claim 3204 now depends from claims 3198, 3199, 3300, 3301, 3326 and 3327, and it recites "*comprising* one or more amines." Thus, earlier reference to "hydroxyls or epoxides" has been deleted from claim 3204.

Similarly, claim 3205 now depends from claims 3198, 3199, 3300, 3301, 3326 and 3327.

Claims 3208 and 3209 similarly now depend from claims 3198, 3199, 3300, 3301, 3326 and 3327, and language reciting "direct or indirect" has been deleted from both claims.

Claim 3210 has been canceled.

Claim 3211 depends from claims 3199 and 3301, and it now recites "wherein *the first strands* of said double-stranded nucleic acids *are* fixed or immobilized to said non-porous solid support *and the other* nucleic acid strands *of said double-stranded nucleic acids are hybridized to said first strands.*" Thus, language for "indirectly," and references to "sandwich hybridization" and complementary hybridization have been deleted from claim 3211.

Claim 3212 depends from claims 3198 and 3300, and it now recites that "said nucleic acids *is* DNA." Claim 3213 depends from claims 3199 and 3301, and it recites that "said nucleic acids *is* DNA."

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 57 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3214 depends from claims 3198 and 3289.

Claim 3215 depends from claims 3199 and 3290.

Claim 3216 depends from claims 3198 and 3300.

Claim 3217 has been amended to depend from claims 3198, 3199, 3300,
3301, 3326 and 3327.

Claim 3218 now depends from claims 3199 and 3290, and it has been
amended by substituting *signaling moiety* for "chemical label."

Claim 3219 now depends from claims 3199 and 3290, and it recites that
the "*non-radioactive signaling moiety* is quantifiable . . . *from* said non-porous solid
support, said quantity being proportional to the amount or quantity of said *non-
radioactive signaling moiety*."

Claim 3220 depends from claims 3199, 3301, 3326 and 3327, and it now
recites that the non-radioactive *signaling moiety* comprises a chromagen or a
chromagenic compound. Other members for the non-radioactive signaling moiety
have been deleted from claim 3220.

Claim 3221 depends from claims 3199, 3301, 3326 and 3327, and it now
recites that "a non-radioactive signal from said non-radioactive *signaling moiety* is
quantifiable or detectable by photometric techniques." In addition to changing
"chemical label" to *signaling moiety*, other techniques have been deleted from claim
3221.

Claims 3222-3223 (Array Having Wells or Depressions)

These claims are also directed to an array with the additional feature that the
non-porous solid support has wells or depressions. Claims 3222 and 3223 are
independent. As amended above, claim 3222 recites "[an] array comprising
various single-stranded nucleic acids fixed or immobilized in hybridizable form to a
non-porous solid support having wells or depressions." Language for "directly or
indirectly" and disclaiming *in situ* has been deleted from claim 3222.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 58 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3223 recites "[an] array comprising various double-stranded nucleic acids fixed or immobilized to a non-porous solid support having wells or depressions, wherein at least one nucleic acid strand of *each of* said various double-stranded nucleic acids comprises at least one non-radioactive *signaling moiety* which is quantifiable or detectable." Thus, in addition to substituting *signaling moiety* for "chemical label," language for "directly or indirectly" and disclaiming *in situ* has been deleted from claim 3223.

The word "claim" in claim 3224 has been pluralized.

Claim 3227 now depends from claims 3222 and 3223, and it recites that the non-porous solid support comprises one or more amines. Language for the "hydroxyls or epoxides" has been deleted from claim 3227.

The word "claim" has been pluralized in claim 3228.

Claims 3231 and 3232 have been amended to delete language for "direct or indirect."

Claim 3233 has been canceled.

Claim 3234 now recites "wherein *the first strands* of said double-stranded nucleic acids *are* fixed or immobilized to said non-porous solid support *and the other* nucleic acid strands *of said double-stranded nucleic acids are hybridized to said first strands*." Thus, language for "indirectly" and references to "sandwich hybridization" and complementary hybridization has been deleted from claim 3234.

Claims 3235 and 3236 now recite that "said nucleic acids *are DNA*."

Claims 3237 and 3238 both recite that the nucleic acids comprise(s) *a gene sequence or pathogen sequence*.

Claim 3239 has been canceled.

The word "claim" has been pluralized in claim 3241.

Claim 3242 now recites "wherein said non-radioactive *signaling moiety* is quantifiable in or from a fluid or solution, said quantity being proportional to the amount or quantity of said *non-radioactive signaling moiety*." Thus, the terms

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 59 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

"chemical label" and "label or labels" have been deleted in favor of the bolded language.

Claim 3243 now recites that the non-radioactive ***signaling moiety*** is quantifiable . . . ***from*** said non-porous solid support, said quantity being proportional to the amount or quantity of said ***non-radioactive signaling moiety***." Thus, language for "in or through," "chemical label," and "label or labels" has been deleted from claim 3243.

Claim 3244 now recites that the "non-radioactive ***signaling moiety*** comprises a chromagen or chromagenic compound." Thus, "chemical label" and other members for the non-radioactive signaling moiety have been deleted from claim 3244.

Claim 3245 recites that "a non-radioactive signal from said non-radioactive ***signaling moiety*** is quantifiable or detectable by photometric techniques." Thus, "chemical label" and other techniques have been deleted from claim 3245.

Claims 3246-3270 (Non-Porous Glass or Non-Porous Plastic Solid Support)

These claims are directed to a non-porous glass or non-porous plastic solid support in which nucleic acid(s) is/are fixed or immobilized to one or more amine(s), hydroxyl(s) or epoxide(s) thereon. Claims 3246 and 3247 are independent.

Claim 3246 now recites "[a] non-porous glass or ***non-porous*** plastic solid support comprising ***one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one single-stranded nucleic acid ***is*** fixed or immobilized in hybridizable form ***to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).***" Thus, the language for "directly or indirectly" and disclaiming *in situ* has been deleted from claim 3246.

In its amended form, claim 3247 recites "[a] non-porous glass or ***non-porous*** plastic solid support comprising ***one or more amine(s), hydroxyl(s) or epoxide(s) thereon, wherein*** at least one double-stranded nucleic acid is fixed or immobilized

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 60 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

to said non-porous glass or non-porous plastic solid support via said one or more amine(s), hydroxyl(s) or epoxide(s), and wherein one nucleic acid strand of said double-stranded nucleic acid has covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety." Thus, language for "directly or indirectly" and disclaiming *in situ* has been deleted from claim 3247.

Claim 3248 has been amended to recite "wherein said non-porous glass or non-porous plastic solid support comprises a plate *or plates*, a well or wells, a microtiter well or microtiter wells, *a depression or depressions, a tube or tubes, a cuvette or cuvettes, or a bead or beads.*"

Claims 3249-3251 have been canceled.

Claims 3252-3254 recite embodiments directed to a surface treatment agent, a blocking agent or both. In each of these claims, the term "non-porous" has been inserted before "plastic" such that the language now reads "non-porous glass or *non-porous* plastic solid support."

Claims 3255-3256 refer to covalent and non-covalent fixation or immobilization. In both claims, the term "non-porous" has been inserted before "plastic" and the phrase "glass or non-porous plastic" has also been inserted before "solid support" near the end of the recitation.

Claim 3257 has been canceled.

In claim 3258, the term "non-porous" has been inserted before "plastic solid support" in two instances. In addition, the phrase "or sequence" has been inserted at the end of the claim.

Claims 3259 and 3260 refer to the nature of the nucleic acid. In addition to the insertion of "non-porous" before "plastic," both claims now recite that "said nucleic acid is DNA."

Claims 3261 and 3262 recite embodiments of the nucleic acid. In both claims, the term "non-porous" has been inserted before "plastic." In the latter, the

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 61 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

language now recites "wherein one strand of said *at least one* double-stranded nucleic acid . . ."

Claims 3263 and 3264 have both been amended to recite "non-porous glass or *non-porous* plastic solid support." This amendment has been made in two instances with respect to claim 3264.

Claims 3265 and 3266 have been amended by substituting "signaling moiety" for "chemical label." The term "non-porous" has been inserted before "plastic solid support." In the case of claim 3266, this substitution has been made in three instances. In accordance with the proposed amendments presented at the February 17, 2005 interview, claim 3266 has also been amended to recite that the non-radioactive signaling moiety "is quantifiable *from* said non-porous glass or non-porous plastic solid support."

Claims 3267 and 3268 refer to more than one single-stranded nucleic acid and more than one double-stranded nucleic acid, respectively. In addition to the insertion of "non-porous" before "plastic solid support" in both claims, the recitation "directly or indirectly" has been deleted.

Claims 3269-3270 have been canceled.

Claims 3271-3286 (Non-Porous Solid Support & System)

Claims 3271-3276 are independent and are each directed to a non-porous solid support. At the beginning of each of claims 3271-3274, the recitation "*one or more amine(s), hydroxyl(s) or epoxide(s) thereon*" has been inserted after "non-porous solid support." Furthermore, all four claims have been amended to state that the variously recited nucleic acid (be it single-stranded nucleic acid, nucleic acid, DNA or RNA) are fixed or immobilized in hybridizable form *to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).*" In addition, the "direct or indirect" language and the *in situ* disclaimer have been deleted from these four claims.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 62 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

In contrast to the aforementioned claims 3271-3274, the *in situ* disclaimer has been maintained in claims 3275 and 3276. In both claims, elements covalently attached to one strand of the double-stranded nucleic acid have been incorporated. Thus, both claims now recite that "one nucleic acid strand of said double-stranded nucleic acid ***has covalently attached thereto either (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety.***" The inclusion of a covalently attached non-radioactive signaling moiety or a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety was discussed at the February 17, 2005 interview.

A minor change (pluralization of "claims") has been effected to claim 3277.

Claim 3278 has been canceled.

Claims 3279-3280 represent two independent system claims. As in the case of the solid support claims 3271-3274 just described, claims 3280 and 3281 have been amended to include "***one or more amine(s), hydroxyl(s) or epoxide(s).***" Further, the "direct or indirect" language and the *in situ* disclaimer have been removed from both claims.

Claims 3281 and 3282 are also independent system claims in which double-stranded nucleic acid is fixed or immobilized to a non-porous solid support. As in the case of the solid support claims 3275 and 3276, claims 3281 and 3282 have been amended so that "***one nucleic acid strand of the double-stranded nucleic acid has covalently attached thereto either (i) a non-radioactive signaling moiety or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety.***" The *in situ* disclaimer has been maintained in both claims.

A minor change (pluralization of "claims") has been effected to claim 3283.

Claims 3284-3286 have been canceled.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 63 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) – May 25, 2005]

To assist in the Examiner's review of the foregoing claim amendments, Applicants' attorney has prepared a table to highlight or summarize the changes in the claims and the support in the specification. This table is attached to this paper as Exhibit B.

New Claims 3287-3407

New claim 3287 was also presented at the February 17, 2005 interview¹ and it has also been added as part of this claim set. This new claim calls for "[a] non-porous solid support comprising at least one double-stranded nucleic acid fixed or immobilized thereto, wherein one nucleic acid strand of said at least one double-stranded nucleic acid has covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety, and wherein said fixation or immobilization is not to a cell fixed *in situ* to said non-porous solid support."

New claim 3288 depends from several other independent claims and it recites the *in situ* disclaimer previously discussed.

Claim 3289 also depends from several other independent claims, and it recites that the non-porous solid support comprises an arrangement of wells, tubes or cuvettes.

Claims 3290 and 3291 are dependent claims directed to surface treatment agents. The former claim recites that the amine providing compound comprises DDA, PPL or 6-aminohexane. The latter claim recites that the acid compound comprises nitric acid.

Claim 3292 relates to the bridging moiety as comprising biotin-avidin, biotin-streptavidin or sugar-lectin.

¹ Claim 3287 was presented as Claim 3145X at the February 17, 2005 interview.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 64 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3293 depends from several claims and recites that one strand of the double-stranded nucleic acid is fixed or immobilized to the non-porous solid support by sandwich hybridization.

Claims 3294-3299 are new dependent system claims. Claim 3294 recites the *in situ* disclaimer previously discussed.

Claim 3295 recites that the non-porous solid support comprises an arrangement of wells, tubes or cuvettes.

Claim 3296 relates to an amine providing compound as comprising DDA, PPL or 6-aminohexane.

Claim 3297 recites that the acid compound comprises nitric acid.

Claim 3298 recites that the bridging moiety comprises biotin-avidin, biotin-streptavidin or sugar-lectin.

Claim 3299 refers to one strand of the double-stranded nucleic acid as being fixed or immobilized to the non-porous solid support and the other strand being hybridized to the one strand.

Claims 3300-3309 are new array claims. Claim 3300 is independent and recites "[a]n array comprising single-stranded nucleic acids fixed or immobilized in hybridizable form to a non-porous solid support." Claim 3301 is also independent and it recites "[a]n array comprising double-stranded nucleic acids fixed or immobilized to a non-porous solid support, wherein at least one nucleic acid strand of said double-stranded nucleic acids comprises at least one non-radioactive signaling moiety which is quantifiable or detectable."

Dependent claim 3302 recites the *in situ* disclaimer.

Claim 3303 recites that the non-porous solid support comprises an arrangement of wells, tubes or cuvettes.

Claim 3304 recites that the amine providing compound comprises DDA, PPL or 6-aminohexane.

Claim 3305 states that the acid compound comprises nitric acid.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 65 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Claim 3306 recites that the non-radioactive signaling moiety is attached to the nucleic acid strand through a bridging moiety. Claim 3307 depends from claim 3306 and recites that the bridging moiety comprises biotin-avidin, biotin-streptavidin or sugar-lectin.

Claim 3308 recites that the double-stranded nucleic acids of the array comprise first strands and second strands, the first strands being fixed or immobilized to the non-porous solid support and the second strands being hybridized to the first strands.

Claim 3309 recites that one strand of the double-stranded nucleic acids is fixed or immobilized to the non-porous solid support by sandwich hybridization.

Claims 3310-3316 are also new dependent claims, but in this instance, the subject matter is directed to an array having wells or depressions as recited in claims 3222 and 3223. Claim 3310 recites the *in situ* disclaimer.

Claim 3311 recites that the non-porous solid support comprises an arrangement of wells, tubes or cuvettes.

Claim 3312 relate to an amine providing compound as comprising DDA, PPL or 6-aminohexane.

Claim 3313 recites that the acid compound comprises nitric acid.

Claim 3314 relates to the non-radioactive signaling moiety as being attached to one nucleic acid strand through a bridging moiety. Claim 3315 depends from claim 3314 and recites that the bridging moiety comprises biotin-avidin, biotin-streptavidin or sugar-lectin.

Claim 3316 depends from claim 3223 and recites that the strand of various double-stranded nucleic acids is fixed or immobilized to the non-porous solid support by sandwich hybridization.

New claims 3317-3323 are directed to dependent embodiments for the non-porous glass or non-porous plastic solid support. Claim 3317 recites the *in situ* disclaimer already discussed above.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 66 [Amendment Under 37 C.F.R. §1.115 (In Response To The November 26, 2004 Office Action) -- May 25, 2005]

Claim 3318 recites that the non-porous glass or non-porous plastic solid support comprises an arrangement of wells, tubes or cuvettes.

Claim 3319 provides that the amine providing compound comprises DDA, PPL or 6-aminohexane.

Claim 3320 recites that the acid compound comprises nitric acid.

Claim 3321 states that the bridging moiety comprises biotin-avidin, biotin-streptavidin or sugar-lectin.

Claim 3322 recites that the non-radioactive signaling moiety comprises a chromagen or chromagenic compound.

Claim 3323 notes that one strand of the double-stranded nucleic acid is fixed or immobilized to the non-porous solid support by sandwich hybridization.

Claims 3324 and 3325 are two new independent solid support claims. Claim 3324 recites "[a] non-porous solid support comprising one or more amine(s), hydroxyl(s) or epoxide(s) thereon, and at least one nucleic acid strand or sequence fixed or immobilized to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s), and wherein another nucleic acid strand or sequence is hybridized to said at least one nucleic acid strand or sequence." Claim 3324 further provides that the "another nucleic acid strand or sequence [has] covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety."

Claim 3325 provides "[a] non-porous solid support comprising at least one nucleic acid strand or sequence fixed or immobilized to said non-porous solid support, and wherein one other nucleic acid strand or sequence is hybridized to said at least one nucleic acid strand or sequence, said other nucleic acid strand or sequence having covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 67 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

attached to a non-radioactive signaling moiety." The rest of claim 3325 recites the *in situ* disclaimer.

Claims 3326 and 3327 are two new independent array claims. In the former, an array comprising various nucleic acid is provided, "wherein single-stranded nucleic acids or sequences are fixed or immobilized to a non-porous solid support, and other single-stranded nucleic acids or sequences are hybridized to said fixed or immobilized single-stranded nucleic acids or sequences, said other nucleic acid strands or sequences comprising at least one non-radioactive signaling moiety which is quantifiable or detectable."

Claim 3327 is directed to "[a]n array comprising various first single-stranded nucleic acids fixed or immobilized to a non-porous solid support, and further comprising second nucleic acids hybridized to said fixed or immobilized first nucleic acids, wherein said second nucleic acids comprise at least one non-radioactive signalling moiety which is quantifiable or detectable."

Claims 3328 and 3329 each depend from solid support claims 3287 and 3325. The former recites that the non-porous solid support comprises one or more hydroxyls. The latter provides that the non-porous solid support comprises one or more epoxides.

Claims 3330 and 3331 are dependent embodiments directed to the nature or form of the non-porous solid support. Claim 3330 recites that the non-porous solid support comprises a plate or plates. Claim 3331 provides that the non-porous solid support comprises a well or wells, a microtiter well or microtiter wells, or a depression or depressions.

Claims 3332-3334 are directed to the nature of the nucleic acid. Claims 3332 and 3333 both recite that the nucleic acid is RNA. Claim 3334 provides that the nucleic acid comprises both DNA and RNA.

Claims 3335-3341 are directed to dependent embodiments for the non-radioactive signaling moiety. These embodiments include a colored dye compound

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 68 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

(claim 3335), a fluorogen or fluorescent compound (claim 3336), a chemiluminescent compound (claim 3337), a chelating compound (claim 3338), an enzyme or enzymatic compound (claim 3339), a coenzyme (claim 3340), and biotin (claim 3341).

Various detection or quantification techniques are set forth in new dependent claims 3342-3345. These include spectrophotometric techniques (claim 3342), colorimetric techniques (claim 3343), fluorometric techniques (claim 3344), and chemiluminescent techniques (claim 3345).

Claims 3346-3361 are directed to dependent embodiments of Applicants' system. Claims 3346 and 3347 provide different embodiments for the nature or form of the non-porous solid support. In claim 3346, the non-porous solid support comprises a plate or plates. In claim 3347, the non-porous solid support comprises a well or wells, a microtiter well or microtiter wells, or a depression or depressions.

Claims 3348-3350 provide embodiments for the nucleic acid. In claims 3348 and 3349, the nucleic acid is RNA. In claim 3350, the nucleic acid comprises both DNA and RNA.

Claims 3351-3357 provide aspects for the non-radioactive signaling moiety. These aspects include a colored dye compound (claim 3351), a fluorogen or fluorescent compound (claim 3352), a chemiluminescent compound (claim 3353), a chelating compound (claim 3354), an enzyme or enzymatic compound (claim 3355), a coenzyme (claim 3356), and biotin (claim 3357).

Various detection and quantification techniques are provided in claims 3358-3361. These include spectrophotometric techniques (claim 3358), colorimetric techniques (claim 3359), fluorometric techniques (claim 3360) and chemiluminescent techniques (claim 3361).

Claims 3362-3395 are new dependent array claims. Claims 3362 and 3363 provide embodiments for the non-porous solid support. In claim 3362, the non-porous solid support comprises a plate or plates. In claim 3363, the non-porous

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 69 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

solid support comprises a well or wells, a microtiter well or microtiter wells, or a depression or depressions.

Reactive sites or binding sites are set forth in new claims 3364 and 3365. The former recites that the non-porous solid support comprises one or more hydroxyls. The latter new claim provides that the non-porous solid support comprises one or more epoxides.

The nature of the nucleic acid is specified in new claims 3366-3368. In claims 3366 and 3367, the nucleic acid is RNA. In claim 3368, the nucleic acid comprises both DNA and RNA.

Aspects of the non-radioactive signaling moiety are provided in claims 3369-3375. These aspects include a colored dye compound (claim 3369), a fluorogen or fluorescent compound (claim 3370), a chemiluminescent compound (claim 3371), a chelating compound (claim 3372), an enzyme or enzymatic compound (claim 3373), a coenzyme (claim 3374), and biotin (claim 3375).

Quantification and detection techniques are specified in new claims 3376-3379. These techniques include spectrophotometric techniques (claim 3376), colorimetric techniques (claim 3377), fluorometric techniques (claims 3378), and chemiluminescent techniques (claims 3379).

Claims 3380 and 3381 provide reactive sites or binding sites. The former claim provides that the non-porous solid support comprises one or more hydroxyls. The latter claim provides that the non-porous solid support comprises one or more epoxides.

Claims 3382 and 3383 provide that the nucleic acids in the array are RNA. Claim 3384 recites that the nucleic acids comprise both DNA and RNA.

The non-radioactive signaling moiety is specified in new dependent array claims 3385-3391. These include a colored dye compound (claim 3385), a fluorescent compound (claim 3386), a chemiluminescent compound (claim 3387), a

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 70 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

chelating compound (claim 3388), an enzyme or enzymatic compound (claim 3389), a coenzyme (claim 3390), and biotin (claim 3391).

Quantification and detection techniques are provided in new claims 3392-3395. These techniques include spectrophotometric techniques (claim 3392), colorimetric techniques (claim 3393), fluorometric techniques (claim 3394), and chemiluminescent techniques (claim 3395).

New dependent embodiments for the non-porous glass or non-porous plastic solid support are set forth in claims 3396-3407. These include the nature or form of the non-porous glass or non-porous plastic solid support in claims 3396 and 3397. In the former, such solid support comprises a plate or plates. In the latter new claim, the solid support comprises a well or wells, a microtiter well or microtiter wells, or a depression or depressions.

Nucleic acid is specified in new claims 3398-3400. In claims 3398 and 3399, the nucleic acid is RNA. In claim 3400, the nucleic acid comprises both DNA and RNA.

The last seven new claims are directed to the non-radioactive signaling moiety which includes a colored dye compound (claim 3401), a fluorescent compound (claim 3402), a chemiluminescent compound (claim 3403), a chelating compound (claim 3404), an enzyme or enzymatic compound (claim 3405), a coenzyme (claim 3406), and biotin (claims 3407).

To facilitate review of new claims 3287-3407, Applicants' attorney has also prepared a second table, the purpose of which is to highlight or summarize support in the specification or previously presented claims that now correspond to the new claims. This second table is attached to this paper as Exhibit C.

As indicated in the table (Exhibit C), in many instances, the new claims are directed to members that were recited together in single claims as "Markush-like" format. These members have now been relegated to separate dependent claims. See, for example, currently amended claim 3166 (now reciting "chromagen or a

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 71 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

chromagenic compound") and new claims 3335-3341 (reciting "colored dye compound," "fluorogen or a fluorescent compound," "chemiluminescent compound," "chelating compound," "an enzyme or enzymatic compound," "a coenzyme," and "biotin," respectively). All eight aforementioned members were previously recited in claim 3166 prior to this paper.

Entry of the above amendments and new claims is respectfully requested.

III. November 26, 2004 Office Action

Turning to the November 26, 2006 Office Action, three separate rejections were lodged against the claims in this application: new matter, vagueness and indefiniteness and anticipation. In the new matter rejection, twelve separate issues have been identified while in the rejection for vagueness and indefiniteness, two separate issues are specified. The single prior art rejection is for anticipation based upon Stuart et al., U.S. Patent No. 4,732,847.

A. The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 3147-3150, 3164-3166, 3170-3171, 3175-3178, 3192-3194, 3198-3245, 3248-3251, 3265-3266, 3269-3270 and 3278 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The text of the written description rejection is set forth on pages 2-8 in the November 26, 2004 Office Action.

The rejection for new matter is respectfully traversed.

In addressing the new matter rejection, Applicants' attorney has separated the points in the rejection into the nine general categories listed below:

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 72 [Amendment Under 37 C.F.R. §1.115 (In Response To The November 26, 2004 Office Action) -- May 25, 2005]

POINTS FROM NEW MATTER REJECTION (11/26/05 OFFICE ACTION)

POINT NUMBER	DESCRIPTION
1	"a plate", "depressions", "beads", a set of plates", "a set of . . . depressions", or "a set of . . . beads".
	A) generic wells
	B) sets vs. arrangements
	C) generic plates
2	"more than one surface"
3	"to one of" said reactive sites or binding sites
4	"proportional to" an amount of label
5	quantifiability "in" or "through" a non-porous solid support
6	"iminobiotin," "hapten" or "ligand" limitation
7	"set" limitations
8	generic array comprising "various" nucleic acids
9	array . . . wells or depressions . . . not <i>in situ</i>

[1] Regarding the citation of "a plate", "depressions", "beads", "a set of plates", "a set of . . . depressions", or "a set of . . . beads" in claims 3147, 3175, 3201 and 3248, Applicants respectfully request the Examiner's consideration of the following remarks. For the sake of convenience, the first issue in the new matter rejection can be reasonably pared down to three sub-issues: generic wells, sets or arrangements, and generic plates.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 73 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

A. generic wells

The Examiner asserts that there is no support for "generic wells." In response, Applicants respectfully point out that *generic* "wells" are disclosed in several different contexts in the specification as follows:

- "plastic or glass wells, . . . (page 13, last line)
- "The portion of the device for containing the fluid is desirably a well, . . . "(page 14, lines 19-20)
- "glass plates provided with an array of depressions or wells . . . "(page 16, lines 10-11)
- "denatured and aliquoted into Dynatech, Immulon II™ removeable wells." (Example 5, page 21, lines 1-2)
- "polystyrene microfilter wells were nitrated" (Example 6, page 22, lines 10-11)
- "The polystyrene wells were immersed" (Example 6, page 22, lines 12-13)
- "Amino-derivitized polystyrene microfilter wells" (Example 6, page 22, lines 28-29)
- "surfaces or wells [of glass or polystyrene surfaces] (Example 6, page 23, line 5)
- "conventional microtiter well plates" (Example 7, page 23, line 17)
- "selected from . . . a well, . . . and an apparatus which comprises a plurality of said wells, . . . " (Original claim 17)
- "selected from . . . a well, . . . " (Original claim 21)

The numerous citations above demonstrate that a *generic* "well" or *generic* "wells" are disclosed in the context of:

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 74 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

- plastic or glass wells
- portion of a device for containing fluid
- glass plates provided with an array of wells
- removable wells
- polystyrene microfilter wells
- polystyrene wells
- wells [of glass or polystyrene surfaces]
- conventional microtiter well plates
- well and a plurality of wells (as set forth in the originally filed claims).²

These several citations above support a "generic well" and "generic wells."

B. sets vs. arrangements

Regarding claims directed to "a set of plates", "a set of . . . depressions", or "a set of . . . beads," (or to state in another way, "sets" vs. "arrangements"), this issue has been obviated by the amendments to claims 3147, 3175, 3201 and 3248. These claims have been amended to recite, "an arrangement of said wells, tubes or cuvettes." Newly submitted claims 3289, 3295, 3303 and 3318 also reflect this amendment. As the examiner pointed out, support for this amendment can be found in the bridging paragraph between pages 13 and 14 as filed.

C. generic plates

The Examiner also asserts that there is no support for "generic plates." In response, Applicants respectfully point out that "plates" are disclosed in five different contexts in the specification as follows:

² During the February 17, 2005 interview, Applicants' attorneys presented the above information as Exhibit 1A.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 75 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

- "glass plates provided with an array of depressions or wells" (Example 1, page 16, lines 9-10)
- "polystyrene plates of different batches" (Example 5, page 20, lines 30-31)
- "... the analyte, was bound to polystyrene plates . . . (Example 5, page 21, lines 17-18)
- "was applied to DDA-coated polystyrene plates." (Example 6, page 22, lines 1-2)
- "conventional microtiter well plates" (Example 7, page 23, line 17) also (Example 7, page 24, second full paragraph).

From the above citations, it is clear that "plates" are disclosed in the context of:

- glass plates with an array of depressions or wells
- polystyrene plates (Petrie dishes)³
- conventional microtiter well plates⁴

These several citations above clearly support a "generic plate" and "generic plates."

[2] Regarding claims directed to "more than one surface," this issue has been obviated by the cancellation of claims 3148, 3176, 3202, 3249 and 3278.

³ The fact that the term "polystyrene plates" constitute flat plastic Petrie dishes was clearly established by the Declaration of Dr. Jannis G. Stavrianopoulos, one of inventors in the present application. See Paras. 14 and 15 of the Stavrianopoulos Declaration submitted with Applicants' June 17, 2002 Supplemental Amendment.

⁴ During the February 17, 2005 interview, Applicants' attorneys presented the above information as Exhibit 1C.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 76 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

[3] Regarding claims directed to "to one of" said reactive sites or binding sites, this issue has been obviated by the cancellation of claims 3149, 3177, 3178, 3250 and 3251.

[4] With respect to the issue of quantitation via a signal which is "proportional to" an amount of label, the original specification clearly provides support for this language which is recited in claims 3164, 3165, 3192, 3193, 3218, 3219, 3242, 3243, 3265 and 3266. The assertion that the specification does not support the "proportional to" limitation is without merit because, at least twice, the specification discloses that the quantification of signal is proportionately generated from a label.

In the first instance found in the last full paragraph on page 4, the specification discloses the term "proportionately" in the context of the primary recognition event and the signalling event of polynucleotide sequence based detection techniques:

The primary recognition event and the signalling event of polynucleotide sequence based detection techniques may be coupled either directly or indirectly, *proportionately* or inversely proportionately. Thus, in such systems as nucleic acid hybridizations with sufficient quantities of radiolabeled probes, the amount of radioactivity is usually *directly proportional to the amount of analyte present*. Inversely proportional techniques include, for example, competitive immuno-assays, wherein the amount of detected signal decreases with the greater amount of analyte that is present in the signal. [emphasis added]

In the second instance, at the end of the first paragraph on page 11, the specification discloses the "quantifiable report of the relative amount of analyte present":

. . . Generation of the soluble signal provides simple and rapid visual detection of the presence of the analyte and also provides a

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 77 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

quantifiable report of the relative amount of analyte present, as
measured by a spectrophotometer or the like. [emphasis added]⁵

The two above-quoted disclosures support the quantitation limitation
directed to the phrase "proportional to" in the claims.

[5] Regarding the issue of quantifiability of a label either "in" or "through" a
"non-porous solid support," the amendments to claims 3165, 3193, 3219, 3243
and 3266 obviate this ground of rejection. These claims now recites "wherein said
non-porous solid support is transparent or translucent, and said non-radioactive
signaling moiety is quantifiable in or from a fluid or solution or *from* said non-porous
solid support . . ."

[6] With respect to the issue of support for the "iminobiotin", "haptten," or
"ligand," limitation in claims 3166, 3194, 3220, and 3244, the deletion of these
members from these claims renders this issue moot and irrelevant.

[7] Regarding the issue of the "set" comprising a support, the cancellation
of claims 3170-3171 and 3269-3270 renders this ground of rejection moot and
irrelevant.

[8] In regard to written description support in the specification for a generic
"array" comprising "various" nucleic acids, Applicants make the following remarks
in response.

⁵ During the February 17, 2005 interview, Applicants' attorneys presented the above information as
Exhibit 4.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 78 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

A. June 30, 2004 Amendment

In the June 30, 2004 Amendment, Applicants added new claims 3198 and 3199, directed to an array comprising "various" nucleic acids fixed or immobilized to a non-porous solid support. It was argued at the time that the specification does not limit the claimed array invention to "different" analytes deposited merely in wells or depression. Applicants pointed out that the specification speaks in several instances to plural sequences, analytes and DNA.⁶ Applicants also submitted the Declaration of Dr. Alexander A. Waldrop, III (hereinafter, "Dr. Waldrop's Declaration" or "the Waldrop Declaration"), who is a person of at least ordinary skill in the art to which the invention pertains.⁷ Dr. Waldrop concludes that the '070 specification reasonably conveys that Applicants were in possession of their claimed array invention, citing as support for his conclusion several passages from the specification.⁸

B. Present New Matter Rejection of Claims 3198-3221

The Office Action rejects claims 3198-3221 on grounds that the specification fails "to reveal any written description of a generic 'array' comprising 'various' nucleic acids. The Office Action acknowledges that the specification includes examples which disclose immobilizing or fixing a "plurality of sequences." However, the Office Action states that the specification does not specify "any

⁶ See, e.g., Original Abstract ("Polynucleotide sequences . . . are detected by a method involving fixing of the sequences on a solid support"); page 10, lines 31-34 ("Chemically labeled probes according to the invention are then brought into contact with the fixed single-stranded analytes under hybridizing conditions"); page 21, lines 21-22 ("To one set of immobilized DNA, no probe was added"); page 23, lines 30-31 ("Single-stranded analyte DNA is now fixed to the wells.").

⁷ See, e.g., Declaration at paras. 2-4 and 12.

⁸ See, e.g., Declaration at para. 14. Dr. Waldrop also provides additional evidence in several other paragraphs in his Declaration as to why the '070 specification does not limit the practice of "various denatured analytes" to an array of depressions or wells. This evidence is presented in paragraphs 15-23.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 79 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

variousness or differences between such pluralities unless also accompanied by requiring depressions or wells." The Office Action further states:

[N]o generic description of arrays as in claim 3198 has been found as filed wherein any specificity as to sequence characterization is set forth without depressions or wells required therefor . . . [N]o array disclosure has been found nor pointed to nor any written support for any array (singular) as claimed in claim 3198 whereon "various" nucleic acids are fixed or immobilized.

The Office Action next addresses Dr. Waldrop's Declaration. In paragraph 15 B (pages 11-12) in his Declaration, Dr. Waldrop avers:

As a person skilled in the art, I read Example 1 and the cited page 16, lines 9-14, as being merely illustrative of one way (depressions or wells) in which nucleic acids can be fixed or immobilized to a non-porous solid support in the form of an array. Because the various surface treatments illustrated in the examples and used to fix or immobilize nucleic acids to non-porous solid supports are not dependent upon the shape or conformation of the support, it is my opinion that Example 1 does not limit Applicants' array practice to depressions or wells. Other aspects of the invention, including the use of other conventional apparatus employed in diagnostic laboratories, such as a plate (for example, a flat Petri dish), a tube, a cuvette, a bead, and the like, are conveyed to me from reading Example 1 and the '070 specification.

According to the latest Office Action, Dr. Waldrop's opinion quoted above is "non-persuasive in that the factual basis on said page 16 corresponds to written support for connecting various nucleic acids with an array having depressions or wells and is thus directed to the limiting written support whereas the opinion expressed in said item # 15 is an allegation which lacks any such factual support." The Office Action dismisses Dr. Waldrop's opinion that the examples do not limit Applicants' array practice to depressions or wells, noting that none of the examples "cite an array with various nucleic acids thereon independent of depressions or wells thus failing to provide written support for the generic array as claimed instantly in claims 3198 etc." The Office Action concludes, "In summary, Declarant's opinion/understanding Declaration fails to provide support for the

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 80 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

written description of an array as now claimed in instant claims 3198-3221 which contain embodiments which are not limited to the combined limitations of various nucleic acids and depressions or wells thereon."

C. Arguments Rebutting the Rejection of Claims 3198-3221

1. Shape of the substrate need not be disclosed in the specification because it is a non-essential claim limitation.

The Office Action purports that claims 3198-3221 lack adequate written description support because the specification does not specify "any variousness or differences between such pluralities unless also accompanied by requiring depressions or wells." The Office Action ignores the fact that whether an array of various nucleic acids is fixed to a non-porous solid support generally, or to depressions or wells specifically, is of little relevance because the shape of the substrate has nothing to do with the novelty of the claimed invention. The novelty resides in the fixing of nucleic acids in hybridizable form to the surface of a substrate, regardless of the shape of the substrate (e.g., flat, curved, etc.).

The case law makes clear that non-critical or conventional features of an invention require no support at all. A description need not be provided for features or elements that are not essential or critical to the invention. (*See, e.g., Ethicon Endo-Surgery, Inc. v. United States Surgical Corporation*, 93 F.3d 1572 (Fed. Cir. 1996)). Further, when broadened claims merely omit an unnecessary or non-critical limitation, a court will most likely conclude that the written description requirement is satisfied. (*See, In re Peters*, 723 F.2d 891 (Fed. Cir. 1983)).

The facts of *In re Peters* are analogous to those of the instant case. In *Peters*, the invention was directed to structural elements of television sets. The original claims recited that the tips of certain elements were tapered. The claims

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 81 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

were later broadened to cover tapered and non-tapered tips. The Examiner rejected the claims as lacking adequate written description support for non-tapered tips, and the Board affirmed. On appeal, the CCPA reversed the Board's decision, holding:

Nor do we agree that the disclosed tip configuration was critical. No prior art was distinguished from and no rejection was overcome on the basis of the tip shape. Most importantly, one skilled in the art would readily understand that in practicing the invention it is unimportant whether the tips are tapered, and the board erred in determining the contrary . . .

The broadened claims merely omit an unnecessary limitation that had restricted one element of the invention to the exact and non-critical shape disclosed in the original patent. In sum, nothing in the original disclosure indicates or suggests that the tapered shape of the tips was essential or critical to either the operation or patentability of the invention. Indeed, if the reissue claims had been submitted with the original application, it is difficult to perceive how they could have been properly rejected under § 112. (*Peters*, 723 F.2d at 893-94)

Like *Peters*, the '070 specification does not describe the substrate shape as essential to the array invention. The shape of the substrate is a conventional feature. It has little or no bearing on the crux of the invention, which is reliably binding nucleic acids to a solid substrate.⁹ There is no technical reason that the substrate has to be a certain shape. Accordingly, the terms "substrate," "support" and "surface" appear in the specification many times, but they are associated with a particular shape only a minority of times, and none of those particular shapes are described as important. Furthermore, substrates of many shapes, including flat substrates with arrays of biological materials on them, were known in the art before the application was filed.¹⁰

⁹ See, e.g., Paper 47, Declaration of Dr. James Stavrianopoulos, section 9:B, pages 8-9.

¹⁰ See, e.g., Chapter 1 of *DNA Arrays: Methods and Protocols*, p. 2, ed. J. Rampal (Humana 2001) ("In the late 1960s, Pardue and Gall (5) and Jones and Robertson (6) discovered a way of locating the position of specific sequences in the nucleus or chromosomes by carrying out the hybridization reaction on cells fixed to microscope slides (in situ hybridization, now more familiarly known as fluorescence in situ hybridization [FISH], following the introduction of fluorescent probes)..."); see

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 82 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Furthermore, the USPTO Written Description Guidelines Training Materials, issued on December 21, 1999, (hereinafter "Training Materials") make clear that claims should not be rejected for lack of adequate written description where the specification fails to recite a non-essential limitation of the claim. Example 2A of the Training Materials concerns the failure to recite an *essential* limitation in the claim:

The specification is directed to artificial hip sockets that include cup implants adapted for insertion into an acetabular, or hip, bone. The specification indicates that the shape of the cup is critical to permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is a trapezoid, a truncated cone, or of conical shape. *All of these terms describe a conical cup. The specification also touts the criticality of a conical cup.... Claim 1 is missing the element of a conical shape.* A review of the specification indicates that a cup implant having a shape which can effectively function as an artificial hip socket is critical to the operation/function of the claimed invention.... [T]he specification indicates that without the conical shape the invention will not operate as intended. Therefore, applicant was not in possession of the necessary common attributes of the elements possessed by the members of the genus. *A written description rejection should be made in this situation.*¹¹ [emphasis added]

Example 2B of the Training Materials concerns the absence in the claim of a *preferred* limitation:

The fact situation of example 2B is similar to example 2A above except that in this example the shape of the conical cup is described as being preferred.... The specification indicates that the shape of the cup must permit the implant to effectively function as an artificial hip socket. The application describes an acetabular cup prosthesis wherein the cup is preferably a trapezoid, a truncated cone, or of

also Paper 47, Declaration of Dr. James Stavrianopoulos, section 16:B, page 37 ("I recall that in carrying out our work with epoxy glues which was eventually incorporated into Example 6 in the '070 specification, my co-inventors and I used more than one type of glass or plastic surface. In particular, we used flat microscope slides (probably glass)....").

¹¹ *Id.* at 15-16.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 83 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

conical shape. All of these terms describe a conical cup.... Claim 1 in the instant application is directed to an acetabular cup prosthesis wherein the shape of the cup is not specifically defined... A review of the specification indicates that a cup implant having a conical shape is preferred but has no apparent bearing to the operation/function of the claimed invention.... Claim 1 is directed to a genus.... The disclosed species is representative of the genus because there is a known correlation between the structure and the function of claimed invention and *one of skill in the art would recognize that applicant was in possession of the necessary common attributes of the elements possessed by the members of the genus*. The invention as claimed will function in its intended manner even without the specific cup shape. *No written description rejection should be made in this situation.* (Training Materials, pgs. 17-18) (emphasis added)

The present fact situation is analogous to Example 2B (preferred limitation), rather than Example 2A (essential limitation). Claims 3198 and 3199 are directed to an array comprising various nucleic acids fixed or immobilized to a non-porous solid support. The Office Action rejects these claims because the specification purportedly fails "to reveal any written description of a generic 'array' comprising 'various' nucleic acids." However, just as the shape of the cup was irrelevant to the function of the invention of Example 2B above, the shape of the solid support (whether part of an array comprising "various" nucleic acids or not) is irrelevant to the function of the present invention. The chemistry of fixing or immobilizing various nucleic acids to a non-porous solid support is the same regardless of whether the various nucleic acids are bound to the surface of a plate or a well, or singly or in an array.¹²

The Office Action, however, would elevate "wells or depressions" to the level of an essential claim limitation. But the Training Materials make clear that a written description rejection should be made only where the criticality of a particular claimed element is touted in the specification, as in Example 2A.

¹² See, e.g., Declaration of Dr. Dollie M. W. Kirtikar, paras. 8 and 11.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 84 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Nowhere does the '070 specification indicate that the shape of the substrate is critical. Indeed, the position of the Office ignores the introductory phrase on page 16, lines 9-14: "*For example*, glass plates provided with an array of wells or depressions would have samples of the various denatured analytes deposited therein, the single-stranded analytes being fixed to the surfaces of the wells." Accordingly, far from emphasizing that substrate shape is critical to the claimed invention, the specification indicates that the substrate may take several shapes, including, "for example," wells or depressions.

2. The specification provides ample support for the claimed "non-porous solid support."

The Office Action states that, while the specification provides support for an array of various nucleic acids fixed to *wells* or *depressions*, it does not disclose an array of various nucleic acids fixed to a generic substrate, i.e., without wells or depressions. As discussed in Section 1 above, because the shape of the substrate is a conventional feature, nothing about its shape need be disclosed in the application or recited in the claims. To the extent that disclosure of the substrate shape is required, however, the Office Action improperly focuses the inquiry on what the specification does not disclose instead of what it *does* disclose. Furthermore, by insisting that the specification only provides support for an array of various nucleic acids fixed to *depressions or wells*, the Office Action ignores the fact that the claims do not recite any particular shape for the substrate. The claims merely recite that the various nucleic acids be fixed to a "*non-porous solid support*." Therefore, the relevant issue is not whether the specification discloses an array of various nucleic acid fixed to every imaginable species of substrate, but whether it discloses an array of various nucleic acids fixed to enough species of substrate to constitute adequate written description support for "non-porous solid support." Furthermore, a particular embodiment appearing in the written description

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 85 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

may not be read into a claim when the claim language is broader than the embodiment. (*See Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048 (Fed. Cir. 1994)).

The Federal Circuit has repeatedly held that claims may be broader than specific embodiments recited in the specification. For instance in *Lampi Corp. v. American Power Products, Inc.*, 56 USPQ2d 1445, 1455 (Fed. Cir. 2000), the court found that disclosure of only identical half-shells was sufficient written description support for a claim encompassing both identical and non-identical half-shells. Indeed, it is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. A specification may, within the meaning of 35 U.S.C. §112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses. Representative samples are not required by the statute and are not an end in themselves. (*See Amgen, Incorporated v. Chugai Pharmaceutical Company, Limited*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991)). A genus typically encompasses many species, often thousands, that are not specifically disclosed in the application. As such, a specification may, within the meaning of 35 U.S.C. §112, 1st para., contain a written description of a broadly claimed invention without describing all species. (*See Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988)). Thus, whether a genus is adequately supported in the specification does not boil down to whether the Examiner can identify a species (e.g., flat substrate) that is not literally recited in the specification but rather whether the disclosed species roughly suggest or round out the scope of the genus. (*See, Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1615 (Fed. Cir. 2002)).

The '070 specification discloses substrates having various shapes, including the following: tubes, cuvettes, plates, wells, plates with wells or depressions, microfilter wells, microtiter plates, "conventional" microtiter wells, solid supports

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 86 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

with "surfaces," plates with "an array" of wells or depressions, "suitable" solid supports, solid supports made of specific non-porous materials such as polystyrene plates (*i.e.*, flat bottom Petri dishes),¹³ solid supports made of specific "conventional" porous materials, a "transparent substrate" that permits "testing of numerous samples," plates with "removeable wells," and supports having "arrangements" of or a "plurality" of wells, and tubes or cuvettes. This disclosure is fairly exhaustive and certainly exceeds the minimum required for a genus as simple and predictable (if not conventional) as the genus "non-porous solid support," particularly when the crux of the invention is the discovery of how to reliably fix or immobilize nucleic acids to any solid material suitable for use in nucleic acid analyses.

Recently in *Bilstad v. Wakalopoulos*, 72 USPQ2d 1785 (Fed. Cir. 2004), the Federal Circuit explained the two commonly recognized exceptions to the rule that disclosure of a species is sufficient written description support for a claimed genus including that species. The claim term in dispute was "plurality," and the issue was whether Bilstad disclosed sufficient species within the "plurality" to meet the written description requirement for count patentability. Bilstad disclosed "a small number of directions." The Board concluded that the count was not patentable to Bilstad.

Reversing the Board on appeal, the Federal Circuit reiterated the well-settled principle that disclosure of *a species* may be sufficient written description support for a later claimed genus including that species. (*Bilstad*, 72 USPQ2d at 1791

¹³ See, Paper 47, Declaration of Dr. James Stavrianopoulos, section 14:C, pages 17-18 (stating that the term "'polystyrene plate' in all instances refers to flat-bottom polystyrene Petri dishes."). To support this conclusion, Dr. Stavrianopoulos provided numerous articles, published before the application was filed, that not only indicate that "'polystyrene plates' [were] recognized in the art to mean flat surfaces unless 'polystyrene plates' is qualified by other descriptions" and that indeed even "'wells' and 'microtiter wells' can take the form of flat bottoms." See, Paper 47, Declaration of Dr. James Stavrianopoulos, section 14:C, pages 17-18. See also Paper 55, Declaration of Dr. James G. Wetmur, section 11, pages 9-10.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 87 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

(emphasis added)). The Court criticized the Board's decision for not discussing whether Bilstad's written description would reasonably convey to a person skilled in the art that Bilstad had possession of the claimed subject matter at the time of filing. (*Id.* at 1792.) In the present case Applicants have provided several declarations addressing the sufficiency of the disclosure.

Reversing the Board on appeal, the Federal Circuit reiterated the well-settled principle that disclosure of a species may be sufficient written description support for a later claimed genus including that species.¹⁴ The Court criticized the Board's decision for not discussing whether Bilstad's written description would reasonably convey to a person skilled in the art that Bilstad had possession of the claimed subject matter at the time of filing.¹⁵ The Court distinguished *In re Curtis*, 354 F.3d 1347 (Fed. Cir. 2004), where claims to a genus of coatings for dental floss were not supported by a species of microcrystalline wax. The *Bilstad* Court stated:

The distinction in these cases is based upon what would be reasonably conveyed to a person skilled in the art at the time of the original disclosure. If the difference between members of the group is such that the person skilled in the art would not readily discern that other members of the genus would perform similarly to the disclosed members, i.e., if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus.¹⁶

The genus in the present case is an array of various nucleic acids fixed to any type of non-porous surface and the species is an array of various nucleic acids fixed to wells or depressions. Borrowing from the language of *Bilstad*, a person skilled in the art *would* readily discern that other members of the genus (e.g., an array of various nucleic acids fixed to a flat surface) would perform similarly to the disclosed members (e.g., wells or depressions). Accordingly, the disclosure of

¹⁴ *Bilstad*, 72 USPQ2d at 1791.

¹⁵ *Id.* at 1792.

¹⁶ *Id.* at 1792.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 88 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

more species is *not* necessary to adequately show possession of the entire genus. This is because it is absolutely irrelevant to the chemistry of attachment whether that non-porous surface is a flat plate, a well or depression, or any other shape. Again, although nucleic acid chemistry might be viewed as unpredictable in certain circumstances, the claim limitation at issue, a non-porous solid support, is conventional.

3. The Office Action fails to afford the necessary weight to Dr. Waldrop's Declaration, which is factually relevant evidence as to issue of possession.

As discussed in Section 2, *supra*, the Office Action impermissibly limits claims 3198-3221 to a non-essential embodiment of a specific example, namely an array of various nucleic acids fixed to *wells* or *depressions*. What's more, Enzo has submitted numerous exhibits and declarations from Ph.D declarants who unanimously and unequivocally state that one skilled in the art would have understood that the '070 specification discloses arrays without regard to specific substrate shapes. Indeed, in his Declaration¹⁷ Dr. Waldrop avers that the '070 specification reasonably conveys that Applicants were in possession of their claimed array invention directed to various nucleic acids fixed to a non-porous solid support.¹⁸

The Office Action fails to afford the necessary weight to Dr. Waldrop's Declaration. The Office Action does not address several points raised by Dr. Waldrop in Paragraph 15A, 15B and 15C, nor does it address points raised in Paragraphs 17-23. Indeed, the Office Action dismisses Dr. Waldrop's statements in Paragraph 15A directed to the phrase "For example," without providing the reasons for doing so. The Office Action thus persists in limiting the specification to

¹⁷ Dr. Waldrop's Declaration was filed concurrently with Applicants' June 30, 2004 Amendment Under 37 C.F.R. § 1.116.

¹⁸ See, e.g., Declaration at paras. 14, 16-23.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 89 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

a specific example, and in particular, to a conventional feature of the specific example. The Office Action further ignores that all of the Examples are characterized as "illustrative of preferred embodiments of the method of the present invention." (See Specification, page 15, lines 6-8) Furthermore, the Office Action dismisses Dr. Waldrop's conclusions as being "non-persuasive," "an allegation which lacks any such factual support," and as "failing to provide support for the written description of an array as now claimed."

By summarily dismissing Dr. Waldrop's conclusions on the issue of adequate written description, the Office Action essentially treats the Declaration as opinion evidence, rather than factual evidence. Indeed, by stating that the Declaration lacks factual support, the Office Action fails to take into account that the Declaration is *itself* factual support. The Office Action suggests that the Declaration does not cure the written description deficiency because it fails to provide the missing written description support. However, the purpose of a Declaration is not to *provide* missing written description support, but rather to *establish* that the existing written description is adequate, i.e., that it conveys possession of the invention to one of skill in the art - a distinct factual question.

Because the Office Action does not read Dr. Waldrop's Declaration in the light of a person skilled in the art who is rendering his opinion on written description, it fails to afford proper weight to the conclusions expressed therein. This is contrary to the overwhelming weight of authority, which holds that declarations are useful factual evidence where adequate written description is at issue.¹⁹ The importance of such declaration evidence was highlighted in *In re Alton*.²⁰ The applicant in *Alton* claimed a variant of IFN- protein in which the first three amino acid residues (two cysteines and a tyrosine) of the wild IFN- protein

¹⁹ See, e.g., *Abbott Labs. v. Syntro Research Inc.*, 67 USPQ2d 1337 (Fed. Cir. 2003); *Union Oil Co. v. Atl. Richfield Co.*, 54 USPQ2d 1227, 1234 (Fed. Cir. 2000); *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

²⁰ *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 90 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

had been deleted and replaced by a single methionine. The Examiner rejected the claims and explained that, although Example 5 discloses substituting a methionine for the first three residues, Example 5 further discloses substituting a lysine for the asparagine at position 81. The Examiner asserted that the claimed modification (substituting a methionine for the first three amino acids) was never disclosed independently of another modification, substituting a lysine for the asparagine at position 81.

The applicant submitted a declaration by an expert, Dr. Wall, who declared that a person of skill in the art would have understood that the applicant possessed the claimed modification independently of the modification at position 81. The Examiner dismissed the declaration, contending that it was "an opinion affidavit on the ultimate legal question at issue." The Board adopted the Examiner's findings. On appeal, the Federal Circuit reversed the Board, holding that the Examiner improperly viewed the Wall declaration as opinion evidence addressing a question of law and summarily dismissed the declaration without explaining why it failed to rebut the *prima facie* case of inadequate description.²¹ The Court stated:

We do not read the declaration as asserting an opinion on the patentability of the claimed IFN- analog. Rather, the declaration is offering factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the modification involving the deletion of the first three amino acids independently of the modification at position 81....²²

The Wall declaration contained statements of fact directly addressing the issue of whether the specification adequately described the subject matter recited in claim 70. The purpose of the adequate written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, *even if every nuance of the claims is not*

²¹ *Id.* at 1174.

²² *Id.*

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 91 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

*explicitly described in the specification, then the adequate written
description requirement is met.*²³ [emphasis added]

The Court continued:

The thrust of the examiner's response to the declaration is that the specification must describe the precise analog claimed.... This argument, however, *does not address the point that the declaration attempts to make*.... The declaration addresses why the claimed subject matter, although not identical to the analog described in the specification, was in the inventor's possession....²⁴ [emphasis added]

The summary dismissal of the declaration without an adequate explanation of why the declaration failed to overcome the *prima facie* case of insufficient description was error.... [The examiner] provided only conclusory statements as to why the declaration did not show that a person skilled in the art would realize that Alton had possession of the claimed subject matter in 1983.²⁵

Like *Alton*, the Office Action in the instant case misapprehends the purpose of Dr. Waldrop's Declaration. The Waldrop Declaration is not asserting an opinion on the patentability of the claimed arrays of various nucleic acids fixed to wells or depressions. Rather, the Waldrop Declaration is offering factual evidence to explain why one of ordinary skill in the art would have understood the specification to describe the claimed arrays. Furthermore, even if Dr. Waldrop's Declaration is treated as merely opinion testimony, the Examiner nevertheless should have considered it. *For instance, in In re Alton*, the Court stated, "In any event, we are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." (76 F.3d at 1175 n.10). The Office Action dismissed Dr. Waldrop's declaration without adequately explaining why it failed to overcome the written description rejection. The Office Action's characterizations of the Waldrop Declaration as "non-persuasive," "an allegation which lacks any such

²³ *Id.* at 1175.

²⁴ *Id.* at 1176.

²⁵ *See Id.* at 1583-84.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 92 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

factual support," and as "failing to provide support for the written description of an array as now claimed," are merely conclusory statements. Such characterizations do not reasonably apprise Applicants of the reasons the Declaration fails to rebut the case of inadequate written description, and thus fail to meet the standard articulated in *Alton*.

In conclusion, the rejection of claims 3198-3221 for inadequate written description is erroneous for several reasons. First, the Office Action ignores the fact that whether an array of various nucleic acids is fixed to a non-porous solid support generally, or to depressions or wells specifically, is of little relevance because the shape of the substrate has little to do with the novelty of the claimed invention, which resides in the fixing of nucleic acids in hybridizable form to the surface of a substrate, regardless of the shape of the substrate (e.g., flat, curved, etc.). The USPTO Written Description Guidelines Training Materials make clear that claims should not be rejected for lack of adequate written description where the specification fails to recite a non-essential limitation of the claim.

Second, by insisting that the specification only provides support for array of various nucleic acids fixed to *depressions or wells*, the Office Action improperly seeks to limit the specification to a specific example, and in particular, to a conventional feature of the specific example. The Federal Circuit has repeatedly held that claims may be broader than specific embodiments recited in the specific specification. Indeed, in the recent case of *Bilstad v. Wakalopoulos*, 72 USPQ2d 1785 (Fed. Cir. 2004), the Federal Circuit reiterated that disclosure of several species is not necessary where the difference between members of the claimed genus is such that a person skilled in the art would readily discern that other members of the genus would perform similarly to the disclosed members.

Finally, the Office Action fails to afford the necessary weight to Dr. Waldrop's Declaration, which must be considered as factually relevant evidence on the issue of adequate written description. In *Alton*, for example, the Federal Circuit

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 93 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

reversed the Board's rejection of a claimed variant of IFN protein on written description grounds. The Court held that the Board had improperly ignored declaration evidence addressing why the claimed subject matter, although not identical to the analog described in the specification, was in the inventor's possession. The Court also held that the Examiner had provided only conclusory statements as to why the declaration did not show that a person skilled in the art would realize that the applicant possessed the claimed subject matter.

[9] Regarding the limitation of a cell fixed *in situ* to wells or depressions as recited in claims 3222-3245, it is believed that the specification clearly discloses this limitation. At the outset, Applicants are mindful that the *in situ* disclaimer language was thoroughly discussed at the May 20, 2004 interview with the Examiner who even suggested minor changes to the proposed language. The fact of the matter is -- indirect fixation techniques, such as *in situ* hybridization and sandwich hybridization, and direct fixation techniques -- are applicable, according to the specification, to fixing nucleic acids to a non-porous solid support. The specification clearly discloses these applications on page 10, first full paragraph:

In accordance with the practice of this invention, analytes in a biological sample are preferably denatured into single-stranded form, and then directly fixed to a suitable solid support. Alternatively, the analyte may be directly fixed to the support in double-stranded form, and then denatured. The present invention also encompasses ***indirect fixation of the analyte, such as in situ techniques where the cell is fixed to the support*** and sandwich hybridization techniques where the analyte is hybridized to a polynucleotide sequence that is fixed to the solid support. . . [emphasis added]

Thus, indirect attachment of nucleic acids, including *in situ* techniques and sandwich hybridization techniques, is applicable to any form of non-porous solid support, be it in the form of a flat surface, such as a polystyrene plate, or curved surfaces, such as wells or depressions. To maintain that "cell fixation *in situ* in

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 94 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

wells or depressions" is not supported flies against the very words in Applicants' disclosure which clearly and unequivocally state that "[t]he present invention also encompasses indirect fixation of the analyte, such as *in situ* techniques where the cell is fixed to the support . . ." Accordingly, the application of the disclaimer language to an array comprising various single-stranded nucleic acids fixed or immobilized to a non-porous solid support having depressions or wells is appropriate and is not new matter because nucleic acids are fixed or immobilized to a suitable solid support as disclosed in the above-quoted passage. In the course of that fixation or immobilization, *in situ* techniques where the cell is fixed to the support is disclaimed.

During the February 17, 2005 interview, Applicants' attorneys presented the above information as Exhibit 9. In view of the above disclosure, it is clear that the specification supports the limitation that the fixation or immobilization is not a cell fixed *in situ* to a non-porous solid support.

In light of the above amendments to the claims and the preceding remarks, it is believed that all grounds of rejection for new matter have been overcome.

B. The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 3144-3286 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Office Action (page 9):

In claims 3170, 3171, 3269, and 3270; a set is claimed but with only one support cited therein regarding said set. Thus, the metes and bounds of the claims are vague and indefinite as to *whether the set is defined by one support or whether the metes and bounds are defined by the set limitation*. Additionally, there is *no indication* in these claims as to *what would be meant if the set includes one or more item(s) other than the cited solid support*. Clarification via clearer claim wording is requested.

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 95 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

All of the presently pending claims, either directly or indirectly via dependence from another claim cite either the phrase "directly or indirectly fixed or immobilized" or "indirectly fixed or immobilized". In the first phrase, it is *unclear whether one, both, or neither of the limitations "directly" or "indirectly" applies to modify "immobilized"*. In the second phrase the *limitation "indirectly" may or may not modify "immobilized"*. The lack of clear and concise metes and bounds of these phrases supports this rejection. Similar phrases, such as "indirect fixation or immobilization" in line 6 of claim 3173 also contain this unclarity.

The indefiniteness rejection is respectfully traversed.

In view of the cancellation of claims 3170-3171 and 3269-3270, the ground of rejection with respect to the "set limitation" has been obviated.

With respect to the phrase "directly or indirectly fixed or immobilized" and "indirectly fixed or immobilized" it is also believed that the matter has been obviated by the above amendments to the claims. Specifically, the claims have been amended to delete the recitation of "directly or indirectly."

Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully urged.

C. The Anticipation Rejection Under 35 U.S.C. §102(e)(2)

Claims 3144-3148, 3151, 3155-3163, 3166-3176, 3179, 3183-3191, 3194-3197, 3246-3249, 3252, 3256-3264 and 3267-3286 stand rejected under 35 U.S.C. §102(e)(2) as being anticipated by Stuart et al., U.S. Patent No. 4,732,847. According to the Office Action (pages 10-11):

Stuart et al. summarizes the usage of monoclonal antibodies for distinguishing DNA-RNA hybrids on a solid surface as disclosed in the abstract. The sample nucleic acid being detected is described in Stuart et al. as being inclusive of detection of specific sequences "from a wide variety of sources" as cited in column 2, lines 30-33. In column 2, lines 48-53, the detection of both naturally occurring as well as synthetic fragments is disclosed. These synthetic analytes are reasonably interpreted as being within the analyte scope of the instant

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 96 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

claims because they are not "cell fixed *in situ*" type as negated in the above listed instant claims. Both covalent and non-covalent fixation of single stranded polynucleotide is cited in column 3, lines 31-40, inclusive also of glass slides which are reasonably interpreted as the commonly utilized non-porous microscope type slides which are well known in the art. Said column 3, lines 31-40, citation also includes disclosure of surface treatment as in instant claim 3151, for example. RNA probes which hybridize to said sample single-stranded nucleic acids are disclosed in column 3, lines 10-21. Antibody detection complexes including non-radioactive labels for detection of hybridized DNA-RNA hybrids are described in column 4, lines 24-55. Thus, the instant claims directed to hybridizable nucleic acids on a non-porous support wherein.

The anticipation rejection is respectfully traversed.

"Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention." (*Electro Med. Sys. S.A. v. Cooper Life Sciences*, 32 U.S.P.Q.2d 1017, 1019 (Fed. Cir. 1994)).

At the outset, Applicants respectfully point out that independent claims 3144, 3145, 3172, 3173, 3246, 3247, 3271, 3272, 3273, 3274, 3279 and 3280 have been amended to recite that the solid support comprises, "one or more amine(s), hydroxyl(s) or epoxide(s) thereon." Stuart et al. 4,732,847 does not disclose a non-porous solid support comprising, "one or more amine(s), hydroxyl(s) or epoxide(s) thereon" wherein a nucleic acid is fixed or immobilized to said non-porous solid support via said one or more amine(s), hydroxyl(s) or epoxide(s).

As discussed above, during the interview of February 17, 2005, the Examiner hypothesized that the glass slide disclosed in Stuart's '847 Patent might provide a hydroxyl group for attaching a nucleic acid. Applicants' representatives and attorneys responded that the SiO₂ present in glass generally could be converted into a functional hydroxyl group capable of bonding to a nucleic acid only by extraordinarily harsh treatment conditions, such as boiling hydrochloric acid (see, for example, Cohen et al., "Covalent attachment of DNA oligonucleotides to glass,"

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 97 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) – May 25, 2005]

Nucleic Acids Research 25(4):911-912 (1997); attached as Exhibit A). Stuart however was completely silent as to such conditions. Indeed, quite to the contrary, Stuart discloses use of a mild acid, such as acetic acid, for treatment of a slide. It is usually safe to assume that persons skilled in the art do not carry out extraordinary treatments, such as use of boiling concentrated HCl unless such conditions are viewed as necessary to achieve a desired end. Accordingly, the inference one can draw by use of such treatment in Cohen et al. certainly supports the idea that a milder and cooler acid would not have sufficed. Therefore, the claims as currently amended are not anticipated by Stuart et al., for at least the above discussed limitations alone or in combination.

Furthermore, independent claims 3145, 3173, 3247, 3275, 3276, 3281 and 3282 have been amended to recite that at least one nucleic acid strand of a double-stranded nucleic acid has "covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety." Accordingly, the claims make clear that the (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety must be covalently attached to at least one nucleic acid strand of a double-stranded nucleic acid.

At best, Stuart discloses the *non*-covalent attachment of a labeled antibody to one nucleic acid strand of a double-stranded nucleic acid. However, Stuart et al. does not disclose a non-porous solid support comprising at least one double-stranded nucleic acid fixed or immobilized to said non-porous solid support, wherein one nucleic acid strand of said double-stranded nucleic acid "has covalently attached thereto either: (i) a non-radioactive signaling moiety, or (ii) a non-radioactive bridging moiety covalently or non-covalently attached to a non-radioactive signaling moiety."

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 98 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

Reconsideration and withdrawal of the 35 U.S.C. §102 rejection is
respectfully requested.

Favorable and early action on this application is respectfully requested.

* * * * *

Enz-7(P)(C3)

Stavrianopoulos et al., U.S. Pat. Appl. Ser. No. 08/486,070 (Filed June 7, 1995)

Page 99 [Amendment Under 37 C.F.R. §1.115 (In Response To The
November 26, 2004 Office Action) -- May 25, 2005]

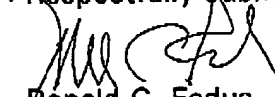
SUMMARY AND CONCLUSIONS

A complete listing of the claims is provided above. Among the claims in the complete listing are new claims 3287-3407.

This amendment is accompanied by a Request for Extension of Time (Three-Months), and authorization for the fee therefor. No other fee or fees are believed to be due in connection with this paper. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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Enz-7(P)(C3)